Blood Pressure Response to Antihypertensive Agents Related to Baseline Blood Pressure

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Abstract

Prevalence of white-coat hypertension varies approximately 20 per cent among mild hypertensives. When white-coat hypertensives are prescribed antihypertensive medication, there is usually a decrease in clinic blood pressure (BP), but little or no change in 24 hours blood pressure (ABPM). The objective of the study was to test the hypothesis that efficacy of medication therapy for hypertension is identical in any grading of severity of baseline blood pressure. The authors retrospectively analysed ABPM data from mild to moderate hypertensive patients. Efficacy in decreasing blood pressure by antihypertensives has linear relation to baseline blood pressure. Response to antihypertensive agents in white-coat hypertension is minimal but a significant effect still persists and the possibility of hypotensive adverse events from medication in the case cannot be overlooked.

Key word : Ambulatory Blood Pressure Monitoring, Hypertension, White-Coat Hypertension, Amlodipine, Mibefradil

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Target BP of 130/85 mmHg or less is recommended by WHO-ISH guideline 1999. To achieve the target, behavioral measures should be followed in all patients. Medications are necessary in patients who cannot obtain target BP with behavioral measures alone(1).

Physicians appreciated BP measurement using the cuff method on each visit (office BP) as a guideline for the adjustment of medication(s) for their patients a long time ago. Recently an electronic blood pressure recorder was introduced and is now well known for ambulatory blood pressure monitoring (ABPM)(2).

As the consequence of ABPM study has become more widespread, a group of patients recognized as having high BP at the office and normal BP at home are known as white-coat hypertension. Medication therapy for white-coat hypertension may not only be unnecessary but may be harmful because of the hypotensive effect from medication(3).

This fearful idea has not yet been comfirmed. A certain number of patients have been treated with antihypertensive agents for many reasons but not for lowering their blood pressure such as propranolol for vascular headache, verapamil for prevention of supraventricular tachycardia and most are used in normotensive patients with good tolerability.

The objective of the study was to test the hypothesis that the efficacy of medication therapy for hypertension is identical in any grading of severity of baseline BP. If the hypothesis is correct, identification for white-coat hypertension is necessary because of the possibility of adverse events from hypotension.

MATERIAL AND METHOD

This study was first designed for comparing efficacy and safety of treatment between mibefradil and amlodipine. Unfortunately, in early 1998 the Roche company decided to withdrew mibefradil from the market. This impact caused early termination of the study.

The present study was conducted according to good clinical practice and was approved by the local ethics committee, and written informed consent was obtained from all patients.

Study patients

The patients considered for the present study participated in a multi-center, randomized, double blinded clinical protocol aimed at comparing the effect of 6-8 weeks treatment with mibefradil 50 mg or amlodipine 5 mg in mild to moderate hypertension. This study was carried out between November 1997 and July 1998.

Study design

Retrospective database analysis of a hypertensive population.

Inclusion criteria were as follows: 1) a new case or previously diagnosed hypertension of mild to moderate degree; between 95-114 mmHg; 2) diastolic BP $\geq$95 mmHg after a placebo run-in period.

Exclusion criteria were as follows: 1) age <20 or >80 yr; 2) treatment with any antihypertensive agent during the study; 3) have atrial fibrillation, associated valvular heart disease, cardiomyopathy; 4) concurrent disease or concomitant therapy that could complicate the drug evaluation or reduce patient compliance e.g. chronic renal failure, cirrhosis, morbid cerebrovascular disease; 5) current pregnancy or lactation; 6) allergy or known hypersensitivity to one of the study drugs; 7) inability to obtain pre-entry diastolic BP (DBP) $\geq$95 mmHg with placebo; 8) for selection into this part of study, only patients who were inadequately controlled by a low dose of each test drug (50 mg of mibefradil and 5 mg of amlodipine) were excluded.

Table 1. Demographic data of patients classified by severity of hypertension and white-coat or true hypertension (sex data from 12 cases were missing).

Group	Male	Female	Age	Total	Mean daytime SBP	Mean daytime DBP
1st Quartile	8	16	58.82 ± 10.40	27	129.89 ± 5.53	84.26 ± 6.23
2nd Quartile	7	14	59.25 ± 8.75	27	144.23 ± 4.05	90.54 ± 5.56
3rd Quartile	9	15	59.30 ± 9.54	27	156.59 ± 2.66	98.16 ± 8.24
4th Quartile	14	12	57.25 ± 11.07	26	167.66 ± 5.97	104.0 ± 9.64
White-coat	1	11	57.40 ± 10.20	14	126.03 ± 4.64	79.52 ± 4.52
True hypertension	37	46	59.06 ± 9.78	93	153.35 ± 12.31	96.93 ± 9.11

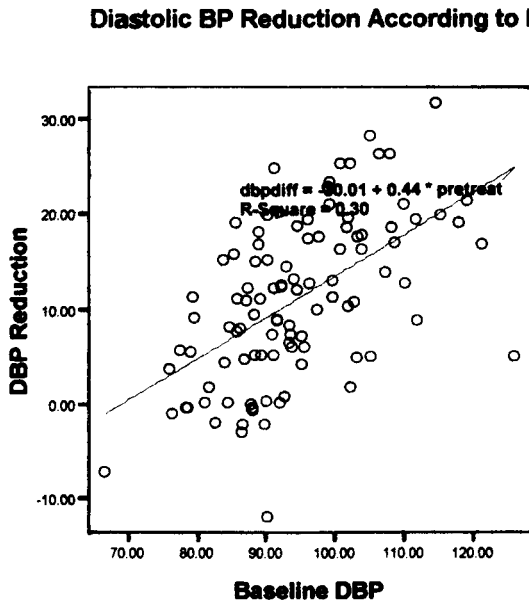

Fig. 1. Diastolic BP reduction related to baseline pretreated diastolic BP.

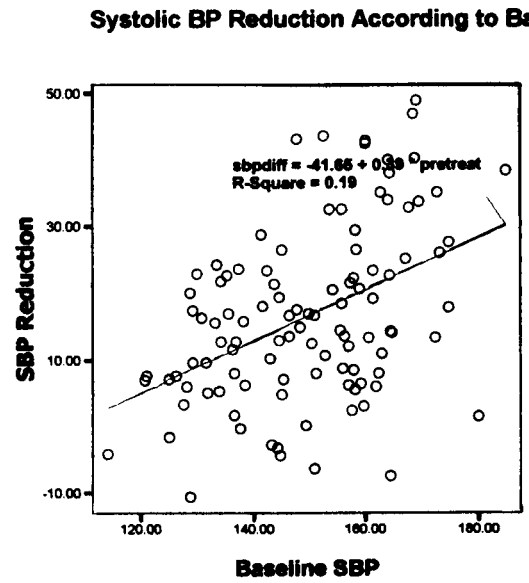

Fig. 2. Systolic BP reduction related to baseline pretreated systolic BP.

Method

Ambulatory blood pressure monitoring (ABPM) study was done in each patient who had DBP ≥95 mmHg after the placebo run-in period. Then subjects were randomized to be given 50 mg mibefradil or 5 mg amlodipine orally once daily. Office BP was appointed 2, 4 and 8 weeks later. Those whose DBP >90 mmHg were given a double dose of the test drug and excluded from this part of the present this study. Compliance was assessed at scheduled visits by tablet count. On the last visit at the 8th week, a second ABPM study was done.

Instrument

Quiettrak model 5100-01 Welch Allyn NC USA was used to measure ABPM. Data recording was analysed using Qtrak software.

Statistical analysis

Mean day-time (7 a.m. to 11 p.m.) systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated. Records were divided into 4 quartiles according to pretreatment day-time DBP. Mean SBP and DBP from each quartile were compared by means of unpaired student *t*-test. Records were also divided into white-coat groups (day-time blood pressure from ABPM study less than 130/85 mmHg) and true hypertension. Mean SBP and DBP from each group were compared in the same way using SPSS pc software 10.0.

RESULTS

Demographic data of each group are presented in Table 1.

Table 2. Pearson correlation between baseline blood pressure, age, sex and blood pressure reduction.

	Pearson Correlation Diastolic BP reduction	Pearson Correlation Systolic BP reduction
Baseline Systolic BP		0.437 (p=0.000)
Baseline Diastolic BP	0.550 (p=0.000)	
Age	-0.278 (p=0.011)	-0.169 (p=0.126)
Sex	0.017 (p=0.867)	0.001 (p=0.993)

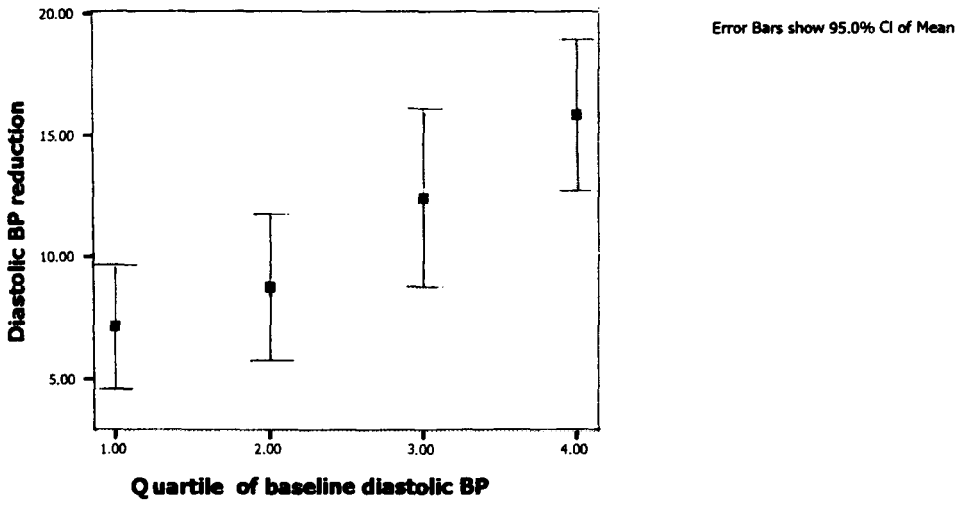

Fig. 3. Response of diastolic BP reduction in each quartile of baseline diastolic blood pressure.

Response of DBP and SBP reduction related to baseline blood pressure are demonstrated in Fig. 1 and 2. Correlation between baseline blood pressure, age, sex and blood pressure reduction is shown in Table 2.

Response of DBP and SBP reduction in each quartiles is demonstrated in Fig. 3 and 4

Diastolic BP reduction between adjacent quartiles determined by independent samples *t*-test are not significantly different from p value between Q1 and Q2 = 0.403, Q2 and Q3 = 0.116, Q3 and Q4 = 0.149 but the reduction of BP is significantly different between Q1 and Q3 (p = 0.019), Q1 and Q4 (p = 0.000), Q2 and Q4 (p = 0.001)

Systolic BP reduction between adjacent quartiles determined by independent samples *t*-test are not significantly different from p value between Q1 and Q2 = 0.321, Q2 and Q3 = 0.115, Q3 and Q4 = 0.065 but the reduction of BP is significantly different between Q1 and Q3 (p = 0.009), Q1 and Q4 (p = 0.000), Q2 and Q4 (p = 0.001)

Response of DBP and SBP reduction in white-coat and true hypertension are demonstrated in Table 3.

DISCUSSION

There is strong evidence from the present study that the efficacy of antihypertensive agents is not identical in lowering blood pressure for different grading of severity of hypertension. Efficacy of treatment is better in higher baseline systolic and diastolic blood pressure.

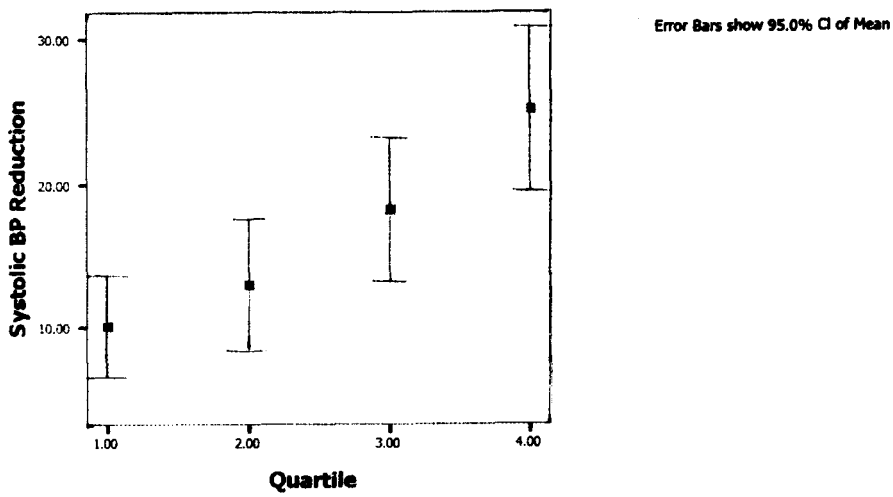

Fig. 4. Response of systolic BP reduction in each quartile of baseline systolic blood pressure.

Table 3. Response of systolic and diastolic BP reduction in white-coat hypertension compared with true hypertension.

	White-coat HT BP reduction	True HT BP reduction	P
Systolic BP	7.62 ± 9.38 mmHg	17.97 ± 13.18 mmHg	0.006
Diastolic BP	3.42 ± 5.65 mmHg	12.41 ± 8.09 mmHg	0.000

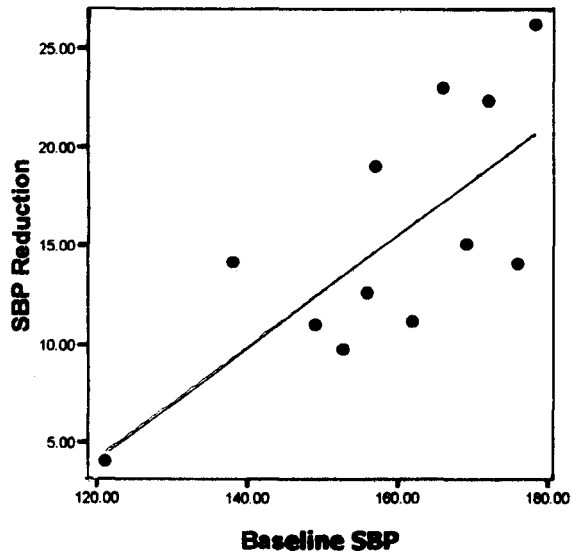

Fig. 5. Systolic blood pressure reduction from study review of 5 mg. Amlodipine therapy corresponding to baseline systolic blood pressure.

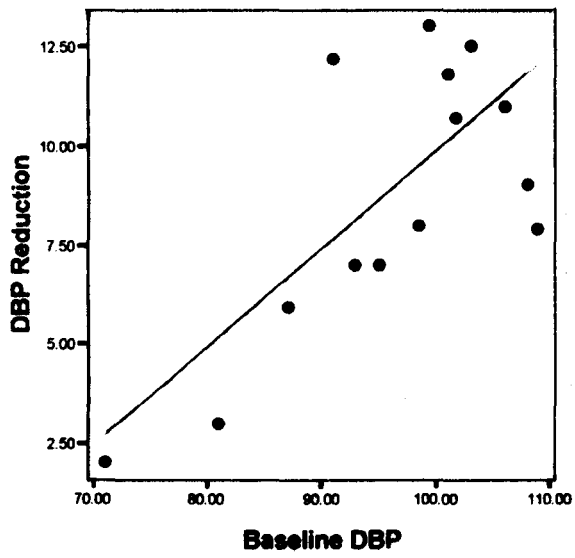

Fig. 6. Diastolic blood pressure reduction from study review of 5 mg. Amlodipine therapy corresponding to baseline diastolic blood pressure.

Studies for efficacy of amlodipine 5 mg in hypertension were reviewed[4-16]. Data from the studies plotted into Fig. 5 and 6 reveal linear correlation in both systolic and diastolic pressure. This finding supports the unidentical response of blood pressure for various baseline blood pressures found in the present study. Oparil et al's[16] is the only one study which separates the mild and moderate hypertension groups with mean DBP 98.5 and 108.9 mmHg. Reduction in DBP was 8 and 7.9 mmHg in the two groups respectively. No other study or antihypertensive agent compared reduction of blood pressure with baseline BP, and so the present study is the first to do so for this category.

Even if the hypotensive effect in white-coat hypertension was lower than that in true hypertension, there was a significant reduction ($p = 0.029$) of blood pressure compared to baseline. This implies that the response to antihypertensive agents in white-coat hypertension is minimal but a significant effect still persists and the possibility of adverse hypotensive events from medication in such a case cannot be overlooked. This may also guide physicians to prescribe antihypertensive agents as a single agent with small dosage and then gradually stepping up the dose.

Because the objective of the present study had to be changed, there are many limitations. 1) 12 missing data for age and sex 2) unidentified concomitant diseases 3) two kinds of active agents were prescribed without being decoded at the end of the study.

SUMMARY

Data of a previous clinical trial was reanalyzed in 107 cases of mild to moderate hypertension treated with low dose mibefradil and amlodipine. Response of blood pressure reduction was found to be better in cases having higher baseline blood pressure. Both systolic and diastolic pressure response behave synchronously in the same pattern. Response in white-coat hypertension was modestly but significantly present. Hypotensive effect from medication, even minimal, cannot be neglected.

Because the original purpose of the present study was not designd for the objective of this analysis, further study directly designed to resolve the same objective is encouraged.

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ความสัมพันธ์ของระดับความดันโลหิตก่อนการรักษาที่มีต่อการลดความดันโลหิต

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ความชุกของความดันโลหิตสูงจากความตื่นเต้นมีประมาณร้อยละ 20 ในผู้ป่วยความดันโลหิตสูงระดับน้อย ผู้ป่วยเหล่านี้จะมีการตอบสนองต่อยาลดความดันโลหิตเมื่อวัดความดันโลหิตในโรงพยาบาลหรือคลินิกแต่เนื่องจากระดับความดันโลหิตเมื่อวัดด้วยเครื่องวัดความดันโลหิต 24 ชั่วโมงจะไม่สูงผิดปกติ ทำให้การรักษาผู้ป่วยกลุ่มนี้ด้วยยาลดความดันโลหิตอาจเกินความจำเป็น วัตถุประสงค์ของการศึกษานี้ต้องการทดสอบสมมุติฐานว่าการตอบสนองต่อยาลดความดันโลหิตในผู้ป่วยความดันโลหิตสูงระดับน้อยถึงปานกลางไม่แตกต่างกันแม้จะมีระดับความดันโลหิตก่อนการได้รับยาที่แตกต่างกัน ผู้วิจัยได้สืบค้นข้อมูลย้อนหลังการรักษาผู้ป่วยความดันโลหิตสูงด้วยยาแอมโลดิพีนขนาด 5 มก และยาไมบีฟราดิล 50 มก และพบว่าการตอบสนองต่อยามีแนวโน้มสัมพันธ์กับระดับความดันโลหิตก่อนการรักษา การตอบสนองต่อยาในผู้ป่วยความดันโลหิตสูงจากความตื่นเต้นแม้จะน้อยแต่แตกต่างจากการใช้ยาหลอกอย่างมีนัยสำคัญและอาจก่อให้เกิดผลไม่พึงประสงค์ที่ควรพึงระวัง

คำสำคัญ : ความดันโลหิต 24 ชั่วโมง, ความดันโลหิตสูง, ความดันโลหิตสูงจากความตื่นเต้น, แอมโลดิพีน, ไมบีฟราดิล

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